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IMMUNE DYSREGULATION IN PEDIATRIC RECURRENT TONSILLITIS: A CASE-CONTROL STUDY ON IMMUNE PROFILES AND INFLAMMATORY MARKERS.

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ABSTRACT

BACKGROUND: Recurrent tonsillitis, characterized by repeated tonsillar inflammation, significantly affects children's quality of life, leading to missed school days, sleep disturbances, reduced participation in daily activities, and emotional distress, and is frequently linked with immune dysfunction. Limited data from developing countries like Pakistan hinders understanding its immunological basis, specifically variations in immune response in the pediatric age group. This study explored the association between recurrent tonsillitis and immune dysregulation to guide diagnosis, treatment, and prevention strategies.

OBJECTIVES: The study aimed to investigate the association between immune dysregulation and recurrent tonsillitis in children focusing on immunological profiles and mechanisms. **STUDY DESIGN**: Case-control study **SETTING & DURATION**: Department of ENT, Hameed Latif Teaching Hospital Lahore, from 25-6- 2024 to 25-11-2024. **METHODS**: In this study, 152 participants were included. Among these participants, 102 children were diagnosed with recurrent tonsillitis cases, and 50 healthy controls of similar age groups were enrolled using consecutive sampling. The calculated sample size at 50% probability, with a 5% margin of error and 95% confidence interval; participants were categorized into specific age groups 3–5, 5–8, 8–10, and 10–12 years to capture variations across different growing ages of Pediatrics. Immune parameters assessed were white blood cell count WBC, neutrophils, lymphocytes, monocytes, eosinophils, plasma IgG, IgA, and IgM levels. Statistical analysis was performed using SPSS version 25, with significance at $p < 0.05$. **RESULTS**: The mean age of participants was 7.5 ± 2.887 years. Children with recurrent tonsillitis had significantly higher WBC counts 12,770 cells/µL in cases vs. 6,500 cells/µL in controls and elevated neutrophil, lymphocyte, and monocyte counts, suggesting heightened immune response. Serum IgG levels were significantly elevated in cases 1330 mg/dL compared to controls 1015 mg/dL, and serum IgA levels were also significantly higher, indicating an ongoing inflammatory response and immune dysfunction. **CONCLUSION**: This study highlights immune dysregulation as a key factor in pediatric recurrent tonsillitis. Elevated WBC, neutrophil, lymphocyte, monocyte counts, and serum IgG and IgA levels suggest elevated inflammatory response. Comprehensive immunological evaluation can aid in adopting preventive and effective strategies for management and prevention.

KEYWORDS: Recurrent Tonsillitis, Immune Dysregulation, Children, Immunoglobulin G IgG, Immunoglobulin A IgA.

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INTRODUCTION

Tonsils are lymphoid structures located at the lateral walls of the oropharynx. They are part of Waldeyer's lymphoid tissue ring, including adenoids and the lingual tonsils. The tonsils produce mucosal immunity by exposure to diverse foods and airborne antigens.[1] Tonsillar tissue serves as a primary barrier of the immune system against numerous micro-organisms that are ingested or inhaled. A variety of bacteria naturally inhabits the mucous membranes of the tonsils and the respiratory tracts, the majority of which compose normal flora.[2] Tonsillitis occurs when antigens bypass the primary barriers of immune defenses and subsequently proliferate rapidly within the tonsillar crypts. Variations in the tonsillar epithelium in recurrent infections can significantly impair antigen processing and immune response activation, referred to as local immunosuppression.[3] According to the 'Paradise Criteria' revised in 2019, tonsillectomy is indicated when overall there are seven attacks of recurrent acute tonsillitis in a year, five or more attacks annually for the previous two years, and three or more attacks annually for the previous three years[4]. Clinically, recurrent tonsillitis is an acute episode of sore throat accompanied by at least one of the following; pain in the throat, fever ≥38.3°C, cervical lymphadenopathy, tonsillar exudate, or a positive microbiological test for group A streptococcus. Tonsillitis is globally regarded as the most prevalent throat disorder in children.[5] In this background, recurrent tonsillitis is predominantly caused by different set of bacteria or viruses that impact the tonsils. Recurrent tonsillitis is more common in children and frequently caused by pathogenic bacteria in children aged five to fifteen years. Kids younger than five years are more likely to develop tonsillitis due to viral infections. School age children are usually infected with the group A streptococcus bacteria.[6] Recurrent tonsillitis is associated with increased production of immunoglobulins Ig, particularly IgA and IgG, in response to repeated antigen exposure, thereby, activating lymphocytes and promoting enhanced cytokine secretion. Blood analysis, including total and differential white blood cell counts can help detect bacterial or viral etiology of these recurrent infections. In addition, in recurrent tonsillitis, there is elevated total leukocyte counts, indicating an active immune response. Any significant rise in the neutrophils counts, highlights bacterial infection in these patients. Neutrophils are powerful phagocytic cells, and play a crucial role in recognizing and phagocytosing the invading microorganisms. In recurrent tonsillitis, bacterial infections simultaneously trigger monocyte migration, raising monocyte counts. IgA is the second most prevalent immunoglobulin protecting the mucosal

surfaces within the tonsillar tissue.[7] A study documents that plasma IgG, IgA, and IgM levels sequentially decrease following tonsillectomy. In contrast, it was found that plasma IgG and IgA levels in patients with recurrent tonsillitis increased, whereas, IgM levels were only slightly increased prior to tonsillectomy procedure.[8] Another study estimated plasma immunoglobulin levels pre and post-operatively, and documented that both IgG and IgM levels were elevated before tonsillectomy attributed to repeated bacterial exposures. It has been shown that IgA levels commonly increase in serum and saliva of children with recurrent tonsillitis. However, IgA levels normalized gradually post-tonsillectomy, while IgM levels dropped negligibly. Although IgG levels showed a significant reduction after surgery, but their levels remained within normal ranges. The concentration of plasma immunoglobulins, particularly IgG, has been linked with the severity of recurrent tonsillitis.[9] Initially, the patients with recurrent tonsillitis under twelve years of age usually remain asymptomatic. But clinically they exhibit a decreased immunoglobulin response and impaired T-cell function, suggesting a genetic predisposition to immune-susceptible recurrent tonsillitis.[10] IgG, which constitutes about 75% of total plasma immunoglobulin concentration, plays a vital role in effectively controlling the tissue infections. On the other hand, IgM, the largest immunoglobulin, rises as a primary response to antigens, and also activates the classical complement pathway, thus further aggravating the inflammatory response. More studies in these lines, have shown significantly elevated levels of IgG, IgA, and IgM in patients with recurrent tonsillitis, indicating their role in defending against pathogens by neutralizing them and activating other components of the immune system.[11]

Pathologically, recurrent tonsillitis frequently leads to tonsillar fibrosis, which exacerbates the process of inflammation and creates a vicious circle that further intensifies the tissue damage. Repeated antigenic stimulation in tonsils leads to increased cytokine synthesis and secretion, particularly Interleukin-1 IL-1β and Tumor Necrosis Factor TNF-α, which characteristically stimulate endothelial and fibroblast proliferation, leading to tissue dysfunction and the replacement of lymphoid tissue by inactive fibrous tissue. Histopathological studies have highlighted aggravated inflammatory damage to the tonsillar tissue in recurrent tonsillitis[12]. After tonsillectomy, some researchers have observed that plasma IgG, IgA and IgM concentrations were significantly lower in patients with recurrent tonsillitis, compared with the control subjects. This finding may be consequent to early restoration of immune response after the surgical removal of chronic antigenic stimulation, thus enhancing the overall function of immune system in the long-term protection against the invading microorganisms.[13] Similarly, another study highlighted the underlying inflammatory mechanism by detecting the neutrophil and plasma cell infiltration in the tonsillar tissue, thus exacerbating the inflammatory damage. Total leucocyte count, absolute neutrophil and lymphocyte counts were significantly raised in patients with recurrent tonsillitis, compared with controls, reflecting general inflammatory response. In these patients, however, monocyte counts showed a slight increase, while eosinophil counts remained stable.[14] Neutrophilia is widely associated with recurrent tonsillitis, with polymorphonuclear neutrophils PMNs migrating to the tonsils via the blood circulation to combat microbial infection. Neutrophils exhibit a driving role in immune defense mecchanisms.[15] It is evident that impaired immune response against chronically infected tonsils contribute to recurrent tonsillitis and resultant tonsillar hypertrophy. The tonsils play a vital role in activation of B

lymphocytes, thereby driving a sequential humoral immune response in these patients. B lymphocytes account for over 50% of tonsillar lymphocytes, compared with lower percentages in blood circulation and soft tissues. WBC count Leukocytosis and ESR are critical indicators of progression of inflammation and predictive tools for tonsillar destruction. [16] The tonsils, part of nasopharyngeal lymphoid tissue NALT, play an important role in localized tissue protection by triggering immune reactions within the respiratory and gastrointestinal systems. Tonsillar infections, therefore, stimulate both humoral and cellular immune responses by activating T-lymphocytes and B-lymphocytes, which differentiate into plasma cells, generating immunoglobulins. These immunoglobulins provide primary protection over the mucosal surfaces IgA. As inflammation progresses, their levels fluctuate; mainly IgA and IgM, increasing overall immunoglobulin concentration against common pathogens causing recurrent tonsillitis.[17]

Aim of this study is to systemically evaluate immune dysregulation in children presenting with recurrent tonsillitis by analyzing total WBC counts, Differential Leukocyte Count DLC Neutrophils, Lymphocytes, Monocytes & Eosinophils, Serum IgG, IgA, and IgM levels. The study is designed to identify potential immune dysregulation that could potentially aggravate tonsillar inflammatory damage in children with recurrent tonsillitis.

MATERIALS AND METHODS

A case-control study was conducted at Hameed Latif Teaching Hospital HLTH Lahore from 25 June 2024 to 25 November 2024. HLTH is a tertiary-care hospital located on the outskirts of Lahore. The calculated sample size at 50% probability, with a 5% margin of error and 95% confidence interval; 152 participants were included in the study. Among these participants, 102 children were diagnosed with recurrent tonsillitis cases, and 50 healthy controls of similar age groups were enrolled using consecutive sampling. All data was obtained from patients reporting in the outdoor ENT department of HLTH.

Inclusion criteria: Children of Ages between 3 years to 12 years with a confirmed diagnosis of recurrent tonsillitis based on clinical confirmation, Paradise criteria and laboratory blood findings.

Exclusion criteria: 1 Patients older than 12 years Distinct and variable immune profiles in adults

2 Children younger than 3 years Immature immune responses

White blood cell counts were estimated in whole blood samples from the patients, stored in EDTA vial, and were freshly analyzed on the automatic hematological analyzer Sysmex 3000

Plasma immunoglobulins were estimated by **turbidimetric immunoassay**, also known as **immunoturbidimetry**, employing Dialab IgG Immunoturbidimetric Assay kit Lot: A00507A, which uses single monoclonal antibody for detection. The immune complexes formed caused the solution to become turbid cloudy; the degree of turbidity was directly proportional to the concentration of the immunoglobulins in the plasma The scattering of light was measured by obtaining its absorbance at 570 nm[18].

Statistical analysis:

The obtained data was entered and analyzed on SPSS version 25. Immune dysregulation in children with recurrent tonsillitis was assessed by immune parameters White blood cell count, Differential leukocyte count and Serum IgG, IgA and IgM levels among the children with recurrent tonsillitis cases and healthy controls. The Chi-Square was employed to assess the association between the recurrent tonsillitis and immune dysregulations based upon the patients' data. P-value <0.05 was considered significant. Patients included in the study were of ages between 3 years and 12 years.

RESULTS:

Patients' Distribution

Among the 152 subjects, 102 children were diagnosed with recurrent tonsillitis and were categorized as cases, whereas, 50 healthy children served as the control group. The mean age of the children was 7.5 ± 2.88 years, ranging from 3 to 12 years. The children were categorized into four age groups. Among cases, 30 children were between 3–5 years, 25 children were between 5–8 years, 25 children were between 8–10 years, and 20 children were between 10–12 years Table 1. Similarly, among controls, 15 children were between 3–5 years, 13 were between 5–8 years, 12 were between 8–10 years, and 10 were between 10–12 years Table 1. The p-values indicate no significant difference between cases and controls in age distribution, ensuring a balanced comparison $p > 0.05$ for all comparisons

Plasma Immunoglobulin IgG, IgM, IgA Levels

The mean plasma IgG levels were 1330 mg/dL in children aged 3–5 years, 1320 mg/dL in those aged 5–8 years, 1127 mg/dL in the 8–10 years group, and 1110 mg/dL in the 10–12 years group, compared with controls, mean IgG level of 1015 mg/dL across all age groups. Similarly, the mean plasma IgM levels were 165 mg/dL, 137 mg/dL, 152 mg/dL, and 140 mg/dL for the respective age groups, with a control IgM level of 126 mg/dL. Mean plasma IgA levels were 266 mg/dL, 182 mg/dL, 160 mg/dL, and 136 mg/dL in the respective age groups, whereas the control IgA level was 137 mg/dL Table 2. These results showed that mean plasma IgG, IgM, and IgA levels were elevated in children with recurrent tonsillitis compared to controls, with statistically significant differences observed across all age groups $p < 0.001$.

Total Leukocyte Count TLC and Differential Leukocyte Count DLC

The mean WBC count was 12,770 cells/µL in children aged 3–5 years, 12,200 cells/µL in 5–8 years, 11,520 cells/µL in 8–10 years, and 10,500 cells/µL in 10–12 years, whereas the control WBC count was 6,500 cells/µL. The mean neutrophil count was 12,220 cells/µL, 9,760 cells/µL, 8,590 cells/µL, and 5,880 cells/µL in the respective age groups, with a control neutrophil count of 4,200 cells/µL. The mean lymphocyte count was 3,880 cells/µL, 3,740 cells/µL, 3,825 cells/µL, and 3,400 cells/µL, compared to a control lymphocyte count of 2,300 cells/µL. The mean monocyte count was 970 cells/µL, 860 cells/µL, 763 cells/µL, and 560 cells/µL, whereas the control monocyte count was 400 cells/µL. The mean eosinophil count was 395 cells/µL, 385 cells/µL, 380 cells/µL, and 390 cells/µL, with a control eosinophil count of 380 cells/µL Table-3. These results indicated a significant increase in WBC, neutrophil, lymphocyte, and monocyte counts in children with recurrent tonsillitis compared to controls $p < 0.001$ for all, while eosinophil counts showed a non-significant increase $p = 0.846$.

Frequency of Recurrent Infections

Among the 102 cases of recurrent tonsillitis, 60% of children experienced more than five episodes per year, while 40% had three to five episodes annually Table-4. The frequency of recurrent infections remained consistent across different age groups, with no statistically significant differences $p = 1.000$. These findings suggest a high burden of recurrent tonsillitis, indicating the need for further investigation into potential immune dysregulation.

Table 1: Age distribution of cases and controls

Age groups of cases years	Cases n=100	Controls n=50	p-values
3 -- 5	30 30%	15 30%	1.000 >0.999
5 -- 8	25 25%	13 26%	0.912
8 -- 10	25 25%	12 24%	0.865
10 -- 12	20 20%	10 20%	1.000 >0.999

Table 2: Immunoglobulin Levels Across Age Groups

Plasma Immunoglobulins	Controls	3–5 years n=30	5–8 years n=25	8–10 years n=25	10–12 years n=20	*P-values*
IgG mg/dL	1015	1330± 50	1320 ± 45	1127 ± 40	1110 ± 35	<0.001
IgM mg/dL	126	165 ± 12	137 ± 10	152 ± 8	140 ± 6	<0.001
IgA mg/dL	137	266 ± 15	182 ± 12	160 ± 10	136 ± 8	<0.001

Table 3: White Blood Cell and Differential Counts Across Age Groups

Blood counts	Control Normal	3–5 yearsn=30	5–8 years n=25	8–10 years n=25	10–12 years n=20	p-value
WBC cells/µL	6500	12770 ± 350	12200 ± 300	11520 ± 280	10500 ± 250	<0.001
Neutrophils cells/µL	4200	12220 ± 320	9760 ± 280	8590 ± 240	5880 ± 200	<0.001
Lymphocytes cells/µL	2300	3880 ± 180	3740 ± 170	3825 ± 150	3400 ± 140	<0.001
Monocytes cells/µL	400	970 ± 40	860 ± 35	763 ± 30	560 ± 25	<0.001
Eosinophils cells/µL	380	395 ± 20	385 ± 15	380 ± 12	390 ± 10	0.846

Table 4: Frequency of Recurrent Infections Across Age Groups Cases Only

Frequency of Infections in cases	3–5 years n=30	5–8 years n=25	8–10 years n=25	10–12 years n=20	Total n=100	*p-value*
3–5 Episodes	12 40%	10 40%	10 40%	8 40%	40 40%	1.000
>5 Episodes	18 60%	15 60%	15 60%	12 60%	60 60%	1.000

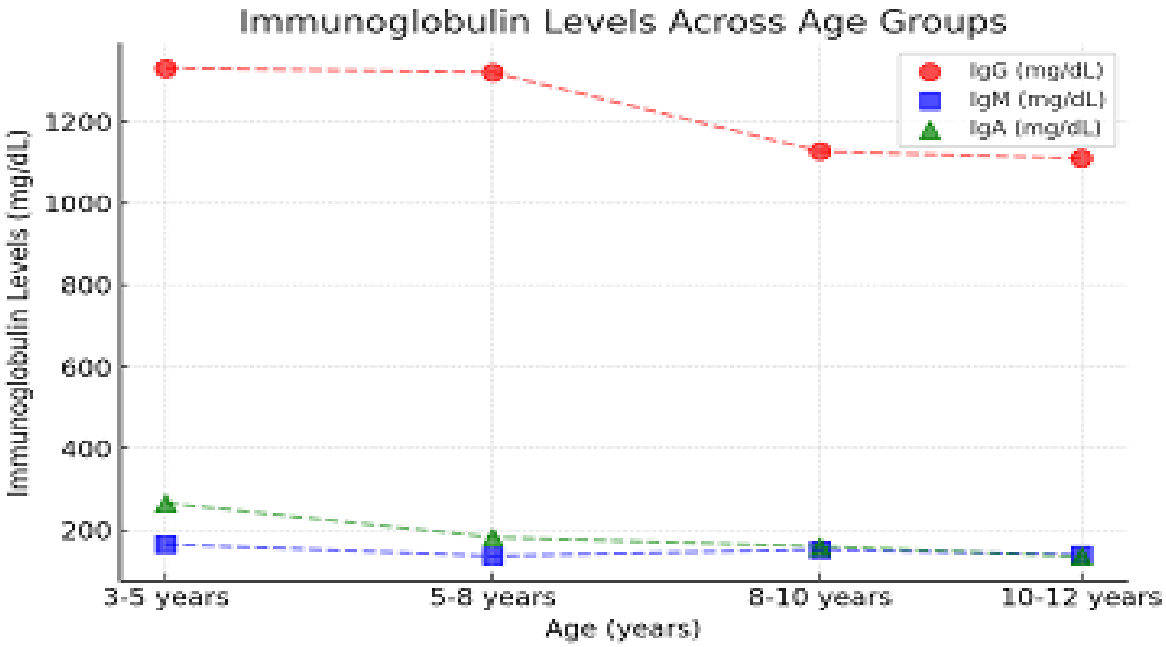

Figure 1: Scatter Plot for Immunoglobulin Levels– Showing trends across different age groups

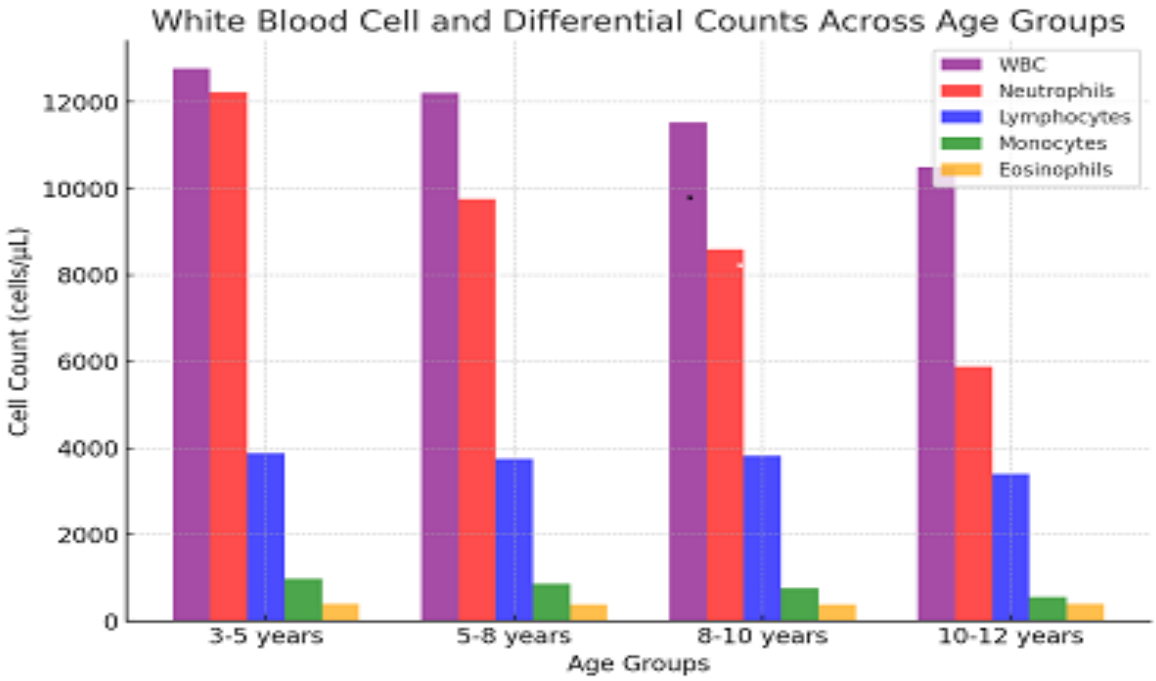

Figure 2: Bar Graph for WBC and Differential Counts: Highlighting differences between age groups

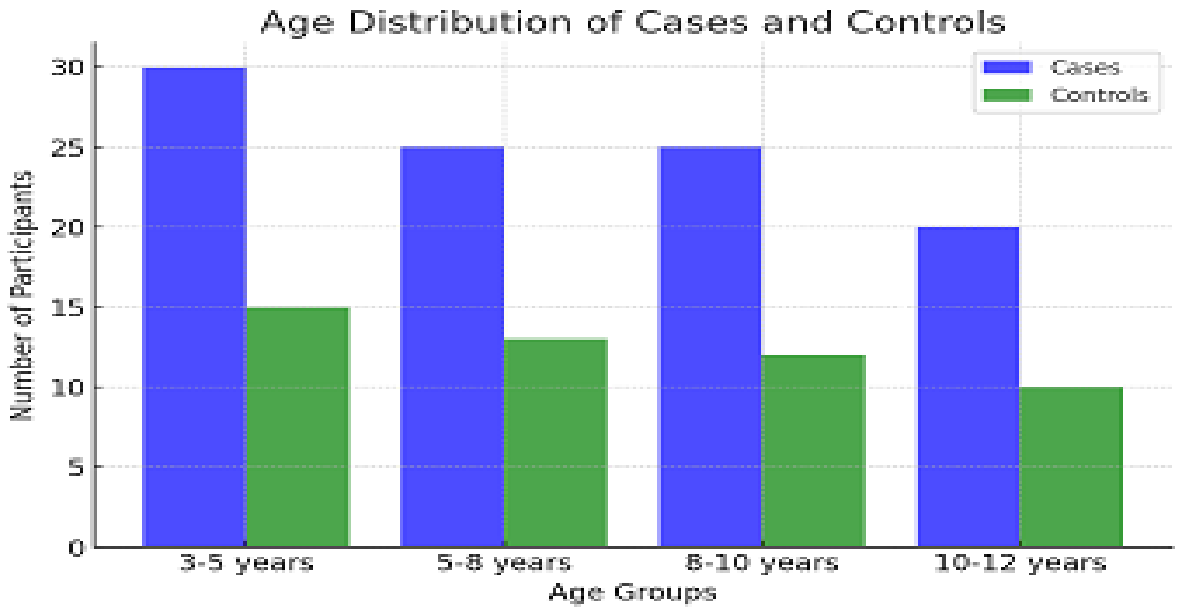

Figure 3: Bar Graph for Age Distribution: Comparing cases and controls across age groups

Discussion

In the current study, 152 pediatric patients with recurrent tonsillitis aged between 3 and 12 years were assessed by measuring serum immunoglobulin levels IgG, IgM, IgA, total leukocyte counts TLC, and differential leukocyte count DLC. These values were compared with healthy control children. The cases were categorized into four age groups: 3–5 years, 5–8 years, 8–10 years, and 10–12 years. The mean age of the patients was $\pm$7.5 years. Mean values of immunoglobulins IgG, IgM, IgA, TLC and DLC were measured for each age group and compared with the controls. Interestingly, it was observed that elevated levels of these blood findings indicated immune dysregulation in children with recurrent tonsillitis. WBC counts are considered important immunological markers which increase in response to recurrent inflammation in tonsillar tissue[6]. The WBC count showed a statistically significant difference in cases of recurrent tonsillitis compared with the controls $p < 0.001$. Specifically, WBC counts in cases were elevated to 12,770 cells/µL compared to 6,500 cells/µL in controls. Neutrophils, lymphocytes, and monocytes also showed significant elevations in cases $p < 0.001$, indicating an ongoing inflammatory damage and resultant immune response. The study results are in line with few research studies, indicating that children with recurrent tonsillitis exhibit elevated serum IgG, IgM and IgA levels. In this study, IgG levels were significantly elevated in cases 1330 mg/dL compared with controls 1015 mg/dL, IgM levels were 165 mg/dL in cases versus 126 mg/dL in controls, and IgA levels were 266 mg/dL in cases versus 137 mg/dL in controls. All differences were highly significant $p < 0.001$, supporting the notion of immune dysregulation in children with recurrent tonsillitis. Although prior to tonsillectomy, these plasma immunoglobulins were slightly elevated, however, in pos-tonsillectomy state, these immunoglobulin levels significantly decrease as the antigenic stimulus is removed and infected tissue is recovered causing appreciably decreased immune response.[19] Blood findings of most children presenting with recurrent tonsillitis exhibited lymphocytosis, monocytosis, and neutrophilia, which are significant cell types in tonsillar tissue inflammation. These raised counts of WBC, lymphocytes, neutrophils, and monocytes correspond to our study findings $p < 0.001$ for all.[20]

Other findings in the study indicated that 60% of children with recurrent tonsillitis experienced more than five episodes annually. The consistent infection frequency across age groups with no statistically significant differences p = 1.000 suggests that immune susceptibility plays a dominant role in the progression of recurrent tonsillitis in susceptible children.

Conclusion

Elevated IgG, IgM, and IgA levels and increased TLC and DLC in pediatric patients with recurrent tonsillitis suggest an aggravated and dysregulated immune response. The results underline the importance of early immunological evaluation, and adopting effective and preventive strategies to reduce the recurrence of tonsillitis in susceptible children.

ETHICS APPROVAL: The ERC gave ethical review approval.

CONSENT TO PARTICIPATE: written and verbal consent was taken from subjects and next of kin.

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AUTHORS' CONTRIBUTIONS:

All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated in the work to take public responsibility of this manuscript. All authors read and approved the final manuscript.

CONFLICT OF INTEREST: No competing interest declared

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